QUALITY OF LIFE AMONG LONG TERM SURVIVORS OF OVARIAN GERM CELL TUMORS

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CERTIFICATE

This is to certify that this dissertation on "**QUALITY OF LIFE AMONG LONG TERM SURVIVORS OF OVARIAN GERM CELL TUMORS"** is a bonafide work done by **Dr. C N Patil,** in the Department of Medical Oncology, College of Oncolgical Sciences, Adyar, Chennai, under my overall supervision and guidance, to my satisfaction

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CONTENTS

INTRODUCTION

In the last two decades, the therapeutic outcomes of ovarian germ cell tumor patients have dramatically improved. Patients with ovarian germ cell tumors who are well staged and whose tumors were initially completely resected and received adjuvant chemotherapy are very often cured.[1] Additionally, ovarian germ cell tumor survivors usually are young and potentially have many years of productive life, if successfully treated. Thus, quality of life issues of long-term survivorship are of great importance.

Ovarian germ cell tumor survivors are a small and unique population of cancer survivors. Although ovarian germ cell tumors occur in older children and younger women, the greatest frequency for diagnosis is in the teens and twenties.[2] Unlike the majority of cancers, germ cell tumors strike during transition from adolescence to adulthood, a time of unique challenges. As treatment begins, concerns related to physical functioning, body image, mood, sexuality, family and vocational pursuits quickly emerge. The young age of women and girls diagnosed with this cancer, coupled with the high survival rates, presents an obligation to

investigate the occurrence of possible long-term physical or psychological sequelae of the cancer itself or the mechanisms used to treat it. Research addressing quality of life issues in ovarian germ cell survivors is limited. Hence we would like to study the quality of life issues in this subset.

AIMS

(1) To analyze the quality of life among Long- Term survivors of ovarian germ cell tumors.

(2) To compare the quality of life between fertility preserved and unpreserved group.

(3) To study the pregnancy outcome in the fertility preserved survivors.

REVIEW OF LITERATURE

Ovarian germ cell tumors (OGCTs) are derived from primordial germ cells of the ovary. They may be benign or malignant. These tumors account for only about 5 percent of all malignant ovarian neoplasms. Malignant Ovarian germ cell tumors (MOGCTs) arise primarily in young women between 10 and 30 years of age; they represent 70 percent of ovarian tumors in this age group.[3]

Clinical Presentation and Initial Evaluation

Several large case series from the 1970s and 1980s provided a detailed description of the clinical presentation associated with MOGCT.[3] These tumors occur principally in girls and young women, with a mean age in the teenage years. Presenting signs and symptoms include abdominal pain and a palpable pelvic-abdominal mass in approximately 85% of patients. Approximately 10% of patients will present with acute abdominal pain mimicking appendicitis, usually caused by rupture, hemorrhage, or torsion of the ovarian tumor. Less common signs and symptoms include abdominal distension(35%), fever(10%), and vaginal bleeding(10%). A small proportion of patients exhibit isosexual precocity related to human chorionic gonadotropin(hCG) production by

the tumor. Many of the OGCT produce serum tumor markers that can serve as an adjunct in initial diagnosis, monitoring during therapy, and post-treatment surveillance. Yolk sac tumor and choriocarcinoma are the prototypes of alpha-fetoprotein (AFP) and hCG production, respectively. Both embryonal carcinoma and polyembryoma may produce hCG and AFP, the former more commonly. A small percentage of dysgerminomas produce low levels of hCG related to the presence of multinucleated syncitiotrophoblastic giant cells, and approximately one third of immature teratomas produce AFP. Of course, mixed germ cell tumors may produce either, both, or none, depending on the type and quantity of elements present. Occasionally, other serum tumor markers, such as lactic dehydrogenase, may be elevated in patients with OGCT, particularly dysgerminoma.

Initial evaluation of a patient with a suspected OGCT based on history and physical examination should include routine blood studies, serum tumor markers, chest x-ray, and imaging studies- pelvic sonography and computed tomography (CT) of the abdomen and pelvis. If dysgenetic gonads are suspected based on physical findings and a history of primary amenorrhea, then karyotyping is indicated.

Pathology

Rare tumors, such as OGCTs, are quite difficult to study. One of the major factors contributing to this situation is the multiplicity of histologic patterns involved and the lack of uniformity in their nomenclature. Thanks to a generation of gynecologic pathologists who focused on these fascinating neoplasms- foremost among whom were Robert E. Scully, H. J. Norris, and Alexander Talerman- a useful classification system began to take shape in the 1970s and has been repeatedly refined to its current state as the 2003 WHO classification system.[4]

Table 1. Classification of Malignant Ovarian Germ Cell Tumors

I. Primitive germ cell tumors
   - A. Dysgerminoma
   - B. Yolk sac tumor
     1. Polyvesicular vitelline tumor
     2. Glandular variant
     3. Hepatoid variant
   - C. Embryonal carcinoma
   - D. Polyembryoma

E. Nongestational choriocarcinoma

F. Mixed germ cell tumor, specify components

II. Biphasic or triphasic teratoma

G. Immature teratoma

H. Mature teratoma

1.Solid

2.Cystic, dermoid cyst

3.Fetiform teratoma, homunculus

III. Monodermal teratoma and somatic-type tumors associated with biphasic or triphasic teratoma

A. Thyroid tumor group

B. Carcinoid group

C. Neuroectodermal tumor group

D. Carcinoma group

E. Melanocytic group

F. Sarcoma group

G. Sebaceous tumor group

H. Pituitary-type tumor group

I. Retinal anlage tumor group

J. Others

Practically, it is most useful to subdivide OGCT into dysgerminoma- the most common type and the counterpart of the male seminoma- and nondysgerminomatous tumors. The most common types of nondysgerminomatous tumors are yolk sac tumor, immature teratoma, and mixed germ cell tumors, with embryonal carcinoma, nongestational choriocarcinoma, and polyembryoma being much less common. n the most recent version of the WHO classification system, OGCTs are divided into three categories: primitive germ cell tumors, biphasic or triphasic teratoma, and monodermal teratoma and somatic-type tumors associated with dermoid cysts. Among the recent advances in our understanding of the pathology of OGCTs are the enhanced recognition of the multiple variants of yolk sac tumor and the CNS tumor group, which can be divided into three distinct categories (differentiated, primitive, and anaplastic) and for which effective therapy appears to differ markedly from the more typical OGCT.[5]

Prognostic factors

Because of the extreme rarity of OGCT, identifying prognostic factors has been quite challenging. However, recent studies have confirmed long standing clinical impressions that the International Federation of

Gynecology and Obstetrics staging system's (FIGO) stage, residual disease, histologic type, and elevation of serum tumor markers appear to be prognostic parameters for patients with OGCT.[6] Lai et al[6] found that advanced FIGO stage and nondysgerminoma/immature teratoma histology were associated with a significantly increased risk of treatment failure, and nondysgerminoma/immature teratoma and bulky residual disease after salvage surgery were significantly associated with a worse overall survival. Murugaesu et al[7] reported that, in univariate and multivariate analyses, in addition to FIGO stage, elevation of both hCG and AFP but not when taken alone, was a strong predictor of survival. Neither study found that age at diagnosis was prognostic.

Management Issues

In general, the treatment principles for all types of malignant ovarian germ cell tumor are similar to those that guide the management of the more common epithelial ovarian cancer (EOC), with some exceptions: Surgery is required for diagnosis, staging, and treatment. As with EOC, the abdomen should be thoroughly explored, with complete surgical staging and optimal cytoreduction when safe and feasible. In contrast to EOC, most OGCTs are stage I at initial presentation, and most patients

can be safely treated with fertility-preserving surgery rather than total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Malignant OGCTs are highly sensitive to platinum-based chemotherapy. This fact, coupled with the poor outcomes from surgery alone (even for stage I disease), has led to routine administration of adjuvant cisplatin-based chemotherapy to most patients except those with stage IA dysgerminoma and well-differentiated stage I immature teratoma.[3]

In contrast to advanced EOC, women with advanced stage OGCTs can often be cured.[3]

Fertility-preserving surgery

Once the diagnosis of a malignant OGCT is confirmed by frozen section, removal of the uterus, both ovaries, and fallopian tubes is suggested for women who have completed childbearing. However, preservation of fertility is often desired since these tumors tend to occur in younger women. Unilateral salpingo-oophorectomy with preservation of a normal-appearing uterus and contralateral ovary is an appropriate procedure in such cases. Even after chemotherapy, at least 80 percent of

these women will resume normal menstrual function, and those who become pregnant appear to have no increase in pregnancy complications.[8]

Late effects of chemotherapy

Although there are substantial data regarding late effects of BEP in men with testicular cancer, sparse information is available for women with OGCTs. Among the long-term adverse events from chemotherapy reported in men who receive cisplatin-based chemotherapy are renal and gonadal dysfunction, neurotoxicity, cardiovascular toxicity, and secondary malignancies. Bleomycin-induced pulmonary fibrosis is also rare but must be kept in mind, particularly if general anesthesia is needed.

Gonadal function

Although ovarian dysfunction or failure is a risk of platinum-based chemotherapy, most women who receive three or four courses of standard dose therapy will recover normal ovarian function, and childbearing is often preserved.[9] In one representative series of 71 patients treated with both fertility sparing surgery and combination

chemotherapy for germ cell malignancies, 62 (87 percent) resumed normal menstruation, and 24 of these women subsequently had 37 offspring.[10] Factors such as older age at initiation of chemotherapy, greater cumulative drug dose, and longer duration of therapy all have an adverse effect on future gonadal function.

Secondary malignancies — An important cause of late morbidity and mortality in patients undergoing treatment for germ cell tumors is the development of secondary malignancies, both solid tumors and leukemia. Etoposide in particular has been implicated in the development of treatment-related leukemias. The chance of developing treatment-related leukemia following etoposide is dose-related. The incidence of leukemia is <0.5 percent in patients receiving a typical three- or four-cycle course of BEP, in which the cumulative etoposide dose is <2000 mg/m^2, compared to as much as 5 percent (representing a 336-fold increase in the likelihood of leukemia) in those receiving more than 2000mg/m^2.[11]

Young women's concerns and quality of life(QOL) issues

Psychological concerns

Many women report perpetual sadness and depressive symptoms after they have been successfully treated for their cancer because of body image concerns, fear of recurrence and post-traumatic stress disorder.[12] Underlying psychiatric illnesses, both diagnosed and undiagnosed, combined with depressed moods, altered self-image and anxiety may also contribute to the development of female sexual dysfunction. Relationship dynamics can change once a woman has a cancer diagnosis. Other worries, which are independent of relationship status, include the threat of disease recurrence, early death, bodily disfigurement, weight changes, finances, employment and insurance.[12]

Table 2. Variables associated with psychosocial adaptation[12]

Social support

Marital status

Living arrangements

Number of family members and relatives in vicinity

History

Substance abuse

Depression

Mental health

Major illness

Current concerns

Health

Religion

Work- finance

Family

Friends

Self appraisal

Others

Education

Employment

Physical symptoms

Ovarian germ cell tumor patients are usually treated successfully and little attention has been directed toward psychological distress that may result from the cancer experience. Thorne (2005) addressed the

prevalence of psychosocial distress in cancer patients and its resulting impact on both the patient's QOL and the health care system which included increased use of health care at all levels.[13] The more confidence a survivor has in her ability to communicate the better long-term QOL outcomes. Additionally, for most cancer patients, health care provider support is an important component of general support.

A body of evidence is emerging that describes the impact of healthcare provider and patient communication on psychosocial distress in cancer survivors. As a result, several studies have directed interventions to increase communication and addressed both the provider and patient.[14]

Fertility issues

Before the 1980s, conventional wisdom held that chemotherapy treatment of a female patient in childhood, adolescence, or young adulthood almost invariably resulted in infertility. Factors such as cumulative drug dose, duration of therapy, and age at treatment were thought to be important in influencing the incidence of ovarian dysfunction.[15] Several reports have documented successful pregnancies in young patients who previously underwent fertility-sparing surgery and

combination chemotherapy for malignant ovarian germ cell tumors.[16,17,18-22] Gerhenson [23] reported a questionnaire study of 40 patients treated for malignant ovarian germ cell tumors in which all patients were successfully treated with fertility-sparing surgery followed by combination chemotherapy; most patients received non-platinum based chemotherapy. At the time of analysis, 33 patients (83 %) were having regular menses. Premature menopause was documented in one patient. Of 16 patients who had attempted pregnancy since chemotherapy, 11 delivered 22 healthy infants, none of whom had major birth defects.

Brewer[17] et al reported their experience with 26 patients treated with surgery plus platinum-based chemotherapy for ovarian dysgerminoma. Of the patients who underwent fertility-sparing surgery and chemotherapy, 71 % maintained their normal menstrual function during and after chemotherapy, and 93% had returned to their prechemotherapy menstrual pattern at the time of the questionnaire. Three subsequent reports have detailed post-therapy reproductive function in patients with malignant ovarian germ cell tumors and have noted normal menstrual

function in at least 80%.[24-26] Several live births were reported in each of these series.

One of the strongest predictors of emotional well-being in cancer survivors, besides sexual function, appearance, and employability, is feeling healthy enough to be a good parent. Cancer survivors are often fearful that their history of cancer or its treatment will have an adverse impact on their offspring by placing them at risk for malignancy, congenital anomalies, or impaired growth and development. They are also concerned about the risks of cancer recurrence, infertility, miscarriage, and achieving a successful pregnancy outcome.

Despite these concerns, surveys have reported that fewer than 60 percent of respondents had received information about fertility after cancer treatment, and even fewer had received information about potential risks to offspring.[27] Others have reported that the rate of elective pregnancy termination among female cancer survivors was higher compared to sibling controls because of the fear that their prior cancer therapy would affect their children.[28] Patient education regarding future reproductive function is thus an important component of the care of individuals with cancer.[29]

Spirituality

One salient aspect of the distress of life threatening or terminal illness is spirituality. Smith and colleagues found that a higher level of spirituality is associated with an increase in the patient's ability to normalize death. In a study of 116 medical oncology outpatients, a significant negative relationship was found between the interaction of spiritual awareness with the patient's personal death perspective and psychosocial distress.[30]

Cognitive- Behavioral interventions

Patients frequently manifest a variety of symptoms as direct effects of cancer and its treatment. Most commonly identified symptoms include acute and chronic pain, anxiety, insomnia, hypochondriasis, anticipatory nausea and vomiting. A variety of cognitive and behavioral interventions can systematically be administered.

Survivorship

A number of studies indicate that while cancer survival may be achieved, it is still a disease that can substantially affect several physical and psychological aspects of a survivor's life. Hypervigilance and

hypochondriasis are common reactions. They experience challenges in four critical life domains

1 Physical health

2 Psychological and social well being

3 Maintaining adequate health insurance and

4 Employment.[31]

Physical health challenges include fear of recurrence, the possibility of second malignancy and other late effects of aggressive treatment. Many survivors actively meet these challenges through preventive regimes of diet, exercise, stress reduction and smoking cessation. In general, most survivors report mild to moderate psychological distress. Cancer Survivors often may be threatened by policy cancellations or reduction in coverage. Employment issues include failure to be promoted, negative attitude towards cancer and undue criticism from supervisors or co-workers.

Assessing quality of life

Approximately 10% of all cancer clinical trials include health related QOL as one of the main end points.[32] Quality of life is a subjective,

multidimensional concept reflecting the patient's perception of all aspects of her health experience.

The domains (areas of behavior or experience) include physical/functional (activity, appearance, appetite, condition, comorbidities, fatigue/sleep/rest disease stage/status genetics, symptoms, and side effects), demographics (age, ethnicity, education, employment, and income), spiritual (hope, meaning/purpose, religion, spirituality), social (family, life events, relationships, roles, sexuality, support), and psychological/cognitive factors (anxiety/fear, depression, body image, control, coping, enjoyment, optimism, perception and interpretation, and prior experience).[33] QOL extends to include performance of everyday activities that reflect well-being, patient satisfaction, functioning and control of disease. Fears and hopelessness clearly play into how people cope with cancer, as do expectations, and the World Health Organization has broadened the definition of QOL to include the context of the culture, personal value systems, goals, standards, and concerns.[34]

QOL measurement in Gynecologic Oncology

Quality of life measurement can provide information about the impact of the disease and its treatment on cancer patients to aid physicians in selecting both anti neoplastic and supportive-care therapy. Several excellent instruments are available to measure health-related QOL in patients with gynecologic cancer. A typical approach combines a generic health status assessment such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire(QLQ) QLQ-C30,[35] or the Functional Assessment of Cancer Therapy-General (FACT-G),[36] with a more targeted set of questions specific to a given tumor type. Basen-Engquist et al. validated a set of questions targeted to ovarian cancer which, when added to the FACT-G, is referred to as the FACT-Ovarian (FACT-O) 12. FACT subscales for cervical and vulvar cancers are also available. The core questionnaire (FACT-G) primarily evaluates the patient's physical, social/family, emotional, and functional wellbeing. The 13-item, ovarian cancer-specific subscale assesses severity of problems that can be addressed through proper disease management.[37] The FACT-O can be used alone or in combination with other scales and subscales of the FACT, such as the FACT/GOG neurotoxicity subscale, if neurotoxicity is of concern, or the Anemia

subscale or Fatigue subscale if one is interested in these specific issues. Another recent addition to an ovarian disease-specific questionnaire module is the QLQ-OV28, developed to supplement the EORTC QLQ-C30. This module incorporates numerous symptoms potentially encountered by ovarian cancer patients (e.g., abdominal, hormonal, sexual).[38] Briefer instruments include the Spitzer and EQ-5D16, 17. Each of these measures provide QOL information relevant to a specific condition for which intervention could be useful, thus potentially improving total patient care.

Clinical implications of QOL Measurement

Managing QOL in gynecologic cancer patients requires careful consideration of all the domains that impact the patient: surgery, and the side effects of chemotherapy and radiotherapy, as well as disease-associated factors that can negatively affect QOL. Prominent among the toxicities and symptoms that can diminish QOL in gynecologic cancer patients are pain, emotional distress, neuropathy, alopecia, nausea and vomiting, anemia, and fatigue.[39] While some investigators remind us that it is impossible to measure a 'sunbeam with a ruler',[40] the systematic development of validated instruments (measures) has allowed important

randomized clinical trials to report QOL. The evolving challenge is translating this advance from clinical trials into clinical practice.

Conclusion

Just as therapy for gynecologic cancer has developed into multimodality care, the impact that cancer treatment has on patients has widened. The gynecologic cancer patient faces many challenges specific to the type of tumor and its treatment, as well as those common to the general oncology population. Recent advances have both improved and challenged QOL. Evaluating and addressing QOL issues is an important part of the whole package of modern medical care. Caring for the patient, as well as her cancer, requires an evolving response and measures to preserve or enhance the quality as well as the quantity of life.

SUBJECTS AND METHODS

Survivors of Germ cell Tumor Ovary, who had completed at least 2 years of follow up after the completion of treatment were included in the study. (From 1995-2005)

Inclusion criteria

1. Pathology proven early or advanced malignant ovarian germ cell tumor.
2. Survivors who were continuously disease-free with minimum follow up of two years at the time of the interview.

Exclusion criteria

1. Patients who had relapsed and received salvage therapy.
2. Patients on palliative therapy.

Methods

Survivors of Ovarian Germ Cell Tumors from 1995-2005 were contacted over phone or letter to review at Out patient clinic. Quality of Life Questionnaire was administered after taking informed consent.

Questionnaire

Two questionnaires were used namely EORTC QLQ-C30 and EORTC OV 28.

Socio demographic variables included age at diagnosis, marital status, level of education and employment status. Medical variables included cancer stage, type of surgery, type of chemotherapy, ovarian function, and child birth after diagnosis.

EORTC QLQ C30 and OV28

The EORTC module QLQ-C30 is a 30 item questionnaire composed of 5 multi item functional subscales : Physical health, role function, emotional function, cognitive function and social functioning; 3 multi item symptom scales measuring fatigue, pain and emesis; a global health scale and 6 items to assess financial impact and general symptoms. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/ QOL represents a high QOL, but a high score for a symptom scale/item represents a high level of

symptomatology/problems. EORTC QLQ- C30 has been validated in Indian patients.[41]

The OV 28 module is designed for patients with local or advanced disease who receive treatment by surgery with or without chemotherapy. It was developed according to the EORTC guidelines. It consists of 28 items assessing abdominal/Gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side effects, hormonal symptoms, body image, attitudes to disease/treatment, and sexuality. EORTC OV 28 module as a supplement to EORTC QLQ C- 30 has been clinically and psychometrically validated.[42]

Survivors completed the questionnaire on their own, however some of them required assistance. Only 7 survivors required assistance by translator and clinical psychologist as 3 were illiterates and the other 4 did not know English.

Statistical Analysis

Scoring of the QLQ-C30 and OV 28 was done according to the procedures described in the EORTC manual.[35] Descriptive and Inferential statistics were used in order to analyze the data using SPSS version 13.

RESULTS

Table 1 Age at Diagnosis

Age (years)	N=50 (%)
1-10	4 (8%)
11-20	21 (42%)
21-30	22 (44%)
31-40	2 (4%)
41-50	1 (2%)

Table 2 Educational Status

Educational Status	N=50
Illiterate	3 (6%)
Primary School	4 (8%)
Secondary School	22 (44%)
Graduation	18 (36%)
Post graduation	3 (6%)

Table 3 Marital Status

At Diagnosis	Current Status			
	Single	**Married**	**Widow**	**Divorce**
Single (N=24)	21	3	0	0
Married(N=24)	0	24	0	0
Widow(N=2)	0	0	2	0
Divorce(N=0)	0	0	0	0

Table 4 Stage at diagnosis

Stage	N=50 (%)
Stage I	22 (44%)
Stage II	3 (6 %)
Stage III	24 (48%)
Staging not possible	1 (2%)

Table 5 Ovary Status

Ovary Status	N=50 (%)
Ovary Preserved	28 (56%)
Ovaries Removed	22 (44%)

Table 6 Menstruation Status

Menstruation Status	N=50(%)
Regained Menstruation	28(56%)
No Menstruation	22(44%)

Table 7 Stage and Total Quality of Life

Stage	N	Mean	SD	P value
I & II	25	90.3316	12.19279	0.107
III	24	79.1638	20.99710	
All stages*	50	84.7456	16.32965	

* Staging was not possible in 1 patient

SD – Standard Deviation

Table 8 Ovary Status and Total Quality Of Life

Ovary Status	N	Mean	SD	P value
Preserved	28	90.4746	15.33648	0.577
Removed	22	77.6482	18.07414	

Table 9 Difference in the different dimensions of QOL among early and advance stage survivors (EORTC QLQ C-30)

Dimensions	Stage	N	Mean	Standard. Deviation	P value
Physical functioning	**I & II**	25	94.4040	11.81064	0.242
	III	24	91.9483	17.69026	
Role functioning	**I & II**	25	96.9992	9.28158	0.384
	III	24	95.8325	11.26332	
Emotional functioning	**I & II**	25	90.4628	15.18585	0.270
	III	24	87.2896	19.60309	
Cognitive functioning	**I & II**	25	94.6632	17.67082	0.315
	III	24	96.8742	9.45968	
Social functioning	**I & II**	25	93.9992	19.02238	0.418
	III	24	90.5100	20.01691	
Financial difficulties	**I & II**	25	3.9996	14.65510	0.004
	III	24	12.4713	25.59279	
Global health status	**I & II**	25	90.3316	12.19279	0.107
	III	24	79.1638	20.99710	

Table 10 Difference in the different dimensions of QOL depending on the ovary status (EORTC QLQ C-30)

Dimensions	Ovary Status	N	Mean	Standard. Deviation	P value
Physical functioning	**Preserved**	28	95.7179	10.91591	0.04
	Removed	22	90.3073	18.37023	
Role functioning	**Preserved**	28	98.5114	6.43793	0.001
	Removed	22	93.9382	13.16167	
Emotional functioning	**Preserved**	28	91.1271	13.83132	0.027
	Removed	22	86.5891	20.92845	
Cognitive functioning	**Preserved**	28	95.2350	16.74480	0.510
	Removed	22	96.5900	9.84849	
Social functioning	**Preserved**	28	97.3207	9.63725	0.517
	Removed	22	86.2382	25.89951	
Financial difficulties	**Preserved**	28	3.5711	13.87427	0.001
	Removed	22	13.6050	26.48040	
Global health status	**Preserved**	28	90.4746	15.33648	0.577
	Removed	22	77.6482	18.07414	

Table 11 Difference in the Symptom scales among early and advance stage survivors (EORTC QLQ-OV28)

Symptom scale	Stage	N	Mean	Standard. Deviation	P value
Abdominal/GI	**I & II**	25	3.3320	6.80210	0.640
	III	24	3.9342	9.75677	
Peripheral neuropathy	**I & II**	25	5.9996	17.26577	0.499
	III	24	4.8600	14.30924	
Hormonal	**I & II**	25	3.3324	8.33150	0.005
	III	24	10.4154	16.15955	
Body image	**I & II**	25	4.6660	12.28432	0.429
	III	24	6.9429	12.92414	
Attitude to disease/treatment	**I & II**	25	17.9972	22.40596	0.854
	III	24	23.6075	22.05275	
Chemotherapy side effects	**I & II**	25	6.9324	12.97771	0.521
	III	24	5.9846	12.14468	

Table 12 Difference in the Symptom scales depending on the ovary status (EORTC QLQ-OV28)

Symptom scale	Stage	N	Mean	Standard. Deviation	P value
Abdominal/GI	**Preserved**	28	2.5782	5.94769	0.093
	Removed	22	4.7968	10.46874	
Peripheral neuropathy	**Preserved**	28	5.3568	16.38764	0.806
	Removed	22	5.3018	14.89298	
Hormonal	**Preserved**	28	1.7850	5.24741	0.005
	Removed	22	14.3923	17.28515	
Body image	**Preserved**	28	4.1661	11.67464	0.205
	Removed	22	7.5741	13.33916	
Attitude to disease/treatment	**Preserved**	28	16.8625	21.66942	0.870
	Removed	22	24.7436	22.46459	
Chemotherapy side effects	**Preserved**	28	5.4754	12.17789	0.726
	Removed	22	7.7405	12.68321	

Table 13 Successful Pregnancies following treatment

Sl. No	Marital status before Rx	Number Of Children		Duration after treatment (years)
		Before Rx	After Rx	
12	Married	1	1	4
17	Married	1	1	3
18	Single	0	1	11
33	Married	0	1	5
39	Married	0	2	2 & 5
44	Married	0	1	1 ½
47	Married	0	1	2
49	Married	0	1	2
50	Single	0	2	1 & 4

Rx- Treatment

Table 14 comparison of Physical functioning and Global health status in OGCT survivors

Scale	Referenced[43]		Referenced[44]		Survivors*	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Physical Functioning	83.65	32.21	78.47	35.77	93.05	18.37
Global Health	74.25	19.44	72.45	21.43	84.74	16.32

* Our Study

RESULTS

100 survivors of Ovarian germ cell tumor treated between 1995 and 2005 were contacted over phone or letter for QOL assessment at out patient clinic. 50 survivors, who had completed minimum 2 years of follow up turned up and were administered the questionnaire after obtaining informed consent.

Demographic Profile

Age at Diagnosis (Table 1).

The mean age at diagnosis was 20.16 years (7- 43 years) with 44 % of the patients between the age group of 21-30 years

The mean age at the time of quality of life analysis was 27.46 years (15-47 years)

Education Status (Table 2)

18 (36%) survivors were pursuing or completed their graduation, 3 were pursuing post graduate education. 4 stopped at primary education level, while only 3 were illiterates.

Marital Status (Table 3)

24 patients were married at the time of diagnosis. Of the 24 unmarried, 3 got married during follow up. 2 were widows at the time of diagnosis. There were no divorces.

Stage and Treatment (Table 4)

50% of the patients had early stage disease, while 48 % had advanced stage. Only 1 patient could not be staged. All except one patient received chemotherapy. Chemotherapy consisted of 3-4 cycles of Bleomycin, Etoposide, Cisplatin (BEP)

Fertility Preservation and Menstrual Status (Tables 5 & 6)

Fertility preservation surgery was possible in 28 patients (56%). All the 28 patients regained their menstrual cycles. Among the 22 in whom contralateral ovary and fertility preservation was not possible, 7 were unmarried with mean age of 26.6 years (18-39 years). Among the ovary preserved group, 15 are still unmarried with mean age of 23 years (15-29 years).

Stage and Total QOL (Table 7)

Total QOL scores were high in both early and advance stage survivors with a mean score of 90.33and 79.16 respectively. Mean score in all the survivors was 84.74.

Ovary Status & Total Quality Of Life (Table 8)

Total QOL score was not statistically significant among fertility preserved and unpreserved group. Both had high scores with a mean of 90.47 and 77.65 respectively.

Difference in different dimensions of quality of life issues (Tables 9 and 10)

There were no statistically significant different scores among early and advance stage survivors except for financial difficulties which was significantly more in advance stage survivors. Physical functioning, role functioning and emotional functioning were significantly better in the fertility preserved group.

Difference in symptom scales (Tables 11 and 12)

Hormonal symptoms were significantly more in advance stage survivors and the ovaries removed group.

Fertility Issues (Table 13)

There were 11 successful deliveries among 9 survivors, with a mean of 3.5 years following completion of treatment. 2 survivors are on treatment for infertility and 15 are still unmarried among the fertility preserved group.

Comparison with published data (Table14)

Means and Standard deviation of QOL outcome variables are comparable with the published data.

DISCUSSION

Ovarian germ cell tumors occur predominantly in the teens and twenties. Majority of them are unmarried or are planning their families. Most of them are educated and have many years of productive life. The purpose of this study was to determine what variables are most closely associated with quality of life outcomes in long-term survivors of ovarian germ cell tumor and also the impact of fertility preservation treatment.

Impact of GCT Ovary on the demographic profile

There was no effect of cancer diagnosis and treatment on the educational status. 2 completed graduation and took up job as teachers and 3 are pursuing post graduate course at the time of administering the questionnaire. Education level was high with 42% having a graduate degree. Only 14% had less than secondary school education. A large study by Victoria Champion et al[44] also noted high education level in Ovarian GCT survivors. Educational level was high, with 47% having a college degree or some graduate school, 29% having some college, and 21% being a high school graduate. Only 3% had less than a high school education in their study.

3 survivors have got married after the completion of treatment. However, a matter of concern was, 7 unmarried patients could not have their ovary preserved and continue to be unmarried. The relatively high percentage of unmarried survivors may be related to survivor age, since more than 40% are less than 25 years old. Marital status could also reflect the lower intimacy motivation which Cella and Tross[45] reported in Hodgkin's disease survivors, which may be related to lower marriage rates and higher divorce rates. This is not the case in our series as all the unmarried survivors are still young and are pursuing education. There were no divorces.

Impact of treatment on quality of life

Although there are substantial data regarding late effects of BEP in men with testicular cancer, sparse information is available for women with Ovarian Germ cell tumors. There were no significant long term treatment related side effects viz., pulmonary toxicity, neuropathy and deafness. Many currently used chemotherapeutic agents can induce significant toxicities, some cumulative or irreversible, that can potentially diminish QOL. Lower education, more menstrual/gynecological symptoms, and presence of cisplatin and bleomycin in the chemotherapy regimen were

significantly associated with greater (worse) neurotoxicity in a study by Victoria Champion et al.[44]A study by National Cancer Institute is currently recruiting survivors to assess the treatment outcome and quality of life in patients with Pediatric Extra-Cranial Germ Cell Tumors Previously Treated on Clinical Trial CCLG-GC-1979-01 or CCLG-GC-1989-01 (NCT00436774).

Impact of stage on Quality of Life score

Both early and advanced stage patients had a high score in total quality of life score. The mean total QOL score was 84.74, which corresponded to high score according to the EORTC questionnaire.[35] Physical functioning, role functioning and emotional functioning were significantly better in in the ovary preserved group.

Hormonal symptoms such as hot flashes and vaginal dryness were significantly more in advance stage survivors. This could be due to bilateral ovariectomy as evident by the same trend in ovaries removed group. There are no studies comparing the QOL issues among early and advance stage survivors of OGCTs. Larger studies with more statistical power are required to confirm our findings.

Financial difficulties were significantly more in advance stage survivors. This could not be further qualified as most of the survivors were from low socioeconomic strata and requires a separate study addressing the social and economic issues.

Means and standard deviations of QOL outcome variables were compared with published data. Scores for this sample were very similar to reports from other populations.[43,44] Therefore it is evident that overall, the ovarian germ cell population was similar to other populations reported in the literature.

Impact of Fertility Preservation

Fertility preserved group had a significantly better general well being and body image. Physical functioning, role functioning and emotional functioning were significantly better in the fertility preserved group.

Hormonal symptoms were significantly more in the ovaries removed group. There were no differences in other variables such as emotional functioning, cognitive functioning and social functioning. There were no differences in the symptom scale among two groups. There are no

studies comparing quality of life issues among ovary preserved and ovaries removed group.

One aspect of quality of life for cancer survivors is the preservation of reproductive-endocrine function and fertility. The specific effects of cancer therapy on reproductive function are not as well understood, and there is no test for fertility except for a resulting pregnancy proving that fertility is maintained.

In our study, all 28 patients who had their fertility preserved had recovery of menstruation. Some authors [23],[46,47] observed that 20-30% of patients with malignant ovarian germ cell tumors treated with both surgery and chemotherapy had disturbed menstrual function, whereas other authors published rates around 10%.[49]

Gerhenson et al[23]. reported on 40 patients with OGCTs treated conservatively, where 68% of the women after completion of chemotherapy maintained regular menses, and 83 % of them were having regular menses at the time of the follow-up. Eleven women

delivered 22 healthy infants, none of whom presented major birth defects.

In contrast to the data in the literature,[10,17,23] 100% survivors had regular menses at the time of interview.

Among the 28 survivors who have undergone fertility sparing surgery, 13 are married. 9 of them have had 11 successful pregnancies. None of them had any difficulty in conceiving, and there is no evidence of birth defects or other disabilities in any of the offspring. The mean duration of conception following completion of treatment was 3.5 years.

In agreement with the rates reported in literature[46,49] 70% survivors have succeeded in conceiving. Another encouraging observation is that 15 (53.57%) are not yet married and are having regular menstrual cycles.
The maintained reproductive potential is not the only issue involved in deciding whether to have children after cancer; other more complex psychological aspects could be involved in such an important decision.

Strengths of the study

Duration of follow-up since chemotherapy is quite long (Mean 7 years) for the majority of survivors.

An attempt to look into various dimensions of quality of life through 2 questionnaires has been made.

Detail analysis of successful pregnancies among fertility preserved group is provided.

Comparison of Quality of life scores among early and advance stage survivors and among fertility preserved and ovariectomised group has been done, which is not reported in literature.

Limitations

1. This was a cross-sectional survey. Our analyses were based on a theoretical model that specified direction, however, only a prospective study could determine if these findings are supported.

2. It is possible that some associations mentioned in this study may have occurred by chance and are not reproducible. It is possible that unknown variables may have confounded results.

CONCLUSIONS

1. The general psychological health and total quality of life is quite good for survivors of ovarian germ cell tumor survivors.

2. Physical and emotional functioning were significantly better in fertility preserved group.

3. Survivors who were rendered menopausal had more hormonal symptoms.

4. The importance of fertility preservation is again emphasized and vigorous efforts to maintain reproductive potential during the initial surgical procedure continues to be warranted.

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BACKGROUND QUESTIONNAIRE

Name	:	
Age	:	
Out Patient No.	:	
Address	:	
Education	:	
Occupation	:	
Marital Status	:	Single/ Married/ Divorced/ Widowed
Number of children	:	
Menstrual Cycle	:	Present/Absent
Date Of Diagnosis	:	
Histopathology	:	
Stage	:	
Treatment given	:	
Date of completion of Treatment	:	
Date of Interview	:	
Interviewer's signature	:	